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Hyperoxaluric nephrolithiasis is a complication of Roux-en-Y gastric bypass surgery

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Roux-en-Y bypass surgery is the most common bariatric procedure currently performed in the United States for medically complicated obesity. Although this leads to a marked and sustained weight loss, we have identified an increasing number of patients with episodes of nephrolithiasis afterwards. We describe a case series of 60 patients seen at Mayo Clinic-Rochester that developed nephrolithiasis after Roux-en-Y gastric bypass (RYGB), including a subset of 31 patients who had undergone metabolic evaluation in the Mayo Stone Clinic. The mean body mass index of the patients before procedure was 57 kg/m^2 with a mean decrease of 20 kg/m^2 at the time of the stone event, which averaged 2.2 years post-procedure. When analyzed, calcium oxalate stones were found in 19 and mixed calcium oxalate/uric acid stones in two patients. Hyperoxaluria was a prevalent factor even in patients without a prior history of nephrolithiasis, and usually presented more than 6 months after the procedure. Calcium oxalate supersaturation, however, was equally high in patients less than 6 months post-procedure due to lower urine volumes. In a small random sampling of patients undergoing this bypass procedure, hyperoxaluria was rare preoperatively but common 12 months after surgery. We conclude that hyperoxaluria is a potential complicating factor of RYGB surgery manifested as a risk for calcium oxalate stones.

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Nearly 20% of the United States population can be currently described as obese (body mass index (BMI) >30 kg/m^2), including 11.5 million who are morbidly obese (BMI >40 kg/m^2).[1] No single dietary therapy or medication has been more than modestly effective for sustainable weight loss. Further, approximately 5 million Americans have what is deemed medically complicated obesity (e.g., weight-related comorbidities such as concurrent diabetes mellitus, hypertension, sleep apnea, and/or other weight-related medical comorbidities). As a consequence, increasing numbers of patients choose surgical interventions to treat their illness, including Roux-en-Y Gastric Bypass (RYGB) procedures, the most common bariatric operation in the United States.[2–7] RYGB procedures result in marked, sustained weight loss and an improvement in abnormal glucose homeostasis, insulin resistance, sleep apnea, hypertension, and cardiovascular risk factors.[8–12] Although both short-term and long-term complications of the RYGB procedure have been recognized, including osteopenia, osteomalacia, and more rarely neurological disorders,[13–19] the procedure has been deemed relatively safe and effective. In a consecutive cohort of 191 RYGB patients from our institution,[20] hospital mortality was 0.5% (1/191), and postsurgical hospital morbidity occurred in 10.5% (20/191) of all patients. Good long-term weight loss was achieved, and patients adapted well to the required new eating habits. Overall, 72% of the patients achieved and maintained a weight loss of 50% or more of their preoperative excess body weight 3 years after the operation. Because RYGB is felt to be a safe, effective, and durable procedure for most patients with medically complicated obesity, in the United States it is considered the procedure of choice for patients receiving bariatric surgery to treat medically complicated obesity. Consequently, in the United States, the number of procedures has increased from an estimated 14 000 in 1998 to 108 000 in 2003.[21]

Until very recently, an increased incidence of renal stones in patients after RYGB procedures had not been appreciated. Furthermore, extensive testing for abnormalities in urine analytes that would characterize those at risk for develop-

ment of nephrolithiasis has not been carried out in patients after RYGB. A small series of 23 patients with hyperoxaluria after RYGB was reported recently from our institution.[22] In this study, we collected detailed metabolic data from a larger cohort of RYGB patients with nephrolithiasis ($n = 60$, including the previous 23 patients), in order to delineate the potential urinary lithogenic factors and response to treatment strategies. To further assess the prevalence and rapidity of onset of potentially lithogenic abnormalities in urine, we conducted a pilot cross-sectional study of urinary oxalate excretion among obese patients before and after RYGB. Our studies show that nephrolithiasis is more common than previously recognized in patients undergoing RYGB surgery, and that abnormalities in the lithogenic profile of urine can occur within 12 months of the procedure in a significant percentage of patients.

RESULTS

Of the 60 patients identified who underwent RYGB and subsequently developed nephrolithiasis, 30 patients were women and 30 were men. Mean time to development of first stone post-RYGB was 2.9 years (range: 1 month–13 years). Twenty-four patients underwent standard RYGB and 36 patients underwent distal RYGB. Because the percentage of patients who undergo the distal procedure at Mayo Clinic is approximately 1/5th that of the standard RYGB (Table 1), the risk of nephrolithiasis may be greater after distal RYGB.

Of these 60 post-RYGB patients with nephrolithiasis, 31 patients had been seen in the Mayo Stone Clinic and therefore had detailed urinary data for further analysis (Table 2 and Figure 1). Among this group, the prevalence of pre-existing nephrolithiasis was relatively high (11/31; 32%). The first patient was seen in 1994, but the majority (17) was

Table 1 | Mayo Clinic, Rochester, nephrolithiasis cases identified after RYGB

	Standard	Distal
Mayo RYGB patients 1985–2004	1178	258
Mayo RYGB patients with Mayo diagnosis codes of nephrolithiasis, oxalate nephropathy, enteric hyperoxaluria (1985–2004)	14	9
Mayo RYGB survey responders with nephrolithiasis events elsewhere (survey sent only to Mayo distal RYGB patients 1985–2004; 168 out of 258 responded)	—	27
Additional Mayo and non-Mayo post-RYGB nephrolithiasis cases identified via stone clinic referrals (through May 2006)	10	0
Total known cases of nephrolithiasis after RYGB seen at Mayo (through May 2006)	24	36
Total nephrolithiasis cases after RYGB with available metabolic data	15	16

RYGB, Roux-en-Y gastric bypass.

Table 2 | 24 h urinary composition in patients presenting with nephrolithiasis after standard and distal RYGB

		RYGB – standard and distal (n=31)		RYGB – standard (n=15)		RYGB – distal (n=16)	
	Reference range	Mean	(s.d.)	Mean	(range)	Mean	(range)
Male/female		14/17		7/8		7/9	
Age	(years)	47.8	(8.2)	49.2	(34-60)	46.3	(30-61)
Time to first stone	(years)	2.2	(2.7)	2.1	(0.2–11.0)	1.9	(2.3.2–7.0)
BMI pre	kg/m^2	57.0	(12.4)	51.8	(41.7–83.8)	62.2*	(49.8–102.7)
Mean BMI loss	kg/m^2	17.5	(8.9)	15.3	(6.2–43.5)	9.9	(19.6–40.3)
no. with stones before		9/31 (29%)		6/15 (40%)		3/16 (21%)	
Volume	(ml)	1612	(687)	1583	(486–2939)	1643	(502–3573)
PH		5.6	(0.6)	5.7	(5.0-6.8)	5.6	(4.8–7.0)
Citrate	$>\sim$400 mg/24 h[#]	394	(361)	518	(0–1176)	269	(0–853)
Oxalate	0.11-0.46 mmol/24 h	0.66	(0.41)	0.61	(0.24–1.19)	0.71	(0.07–1.80)
Calcium	20–275 mg/24 h	132	(96)	115	(37–241)	149	(43–504)
Uric Acid	$<$750 mg/24 h	456	(207)	479	(213–708)	435	(153–1002)
Magnesium	75–150 mg/24 h	98	(47)	100	(31–227)	96	(40–149)
Phosphorous	$<$1100 mg/24 h	893	(450)	717	(38–1513)	1069*	(610–2059)
Sodium	40–217 mmol/24 h	180	(76)	168	(74–396)	192	(86–299)
Potassium	30–90 mmol/24 h	43	(18)	38	(24–56)	46	(21–90)
Chloride	10–250 mmol/24 h	162	(56)	144	(75–209)	170	(58–265)
Sulfate	$<$47 mmol/24 h	12.1	(5.2)	12.6	(6.0–24.0)	12.1	(4.0–24.0)
CaOx SS	$<$1.77 DG[a]	2.23	(0.52)	2.02	(1.14–2.84)	2.34	(1.72–2.92)
BR SS	$<$0.21 DG[a]	−1.47	(1.56)	−1.41	(−2.75-0.31)	−1.49	(−5.22–1.10)
UA SS	$<$1.04 DG[a]	0.83	(3.40)	0.81	(−4.73–4.51)	0.85	(−6.27–4.64)
Creat Clearance	(ml/min)	89	(25)	99	(75–145)	83	(49–124)

BMI, body mass index; BR, brushite; CaOx, calcium oxalate; DG, delta Gibbs unit; RYGB, Roux-en-Y gastric bypass; SS, supersaturation; UA, uric acid.
[a]DG is negative for undersaturated solutions, and positive for saturated solutions. Any value greater that the reference mean is considered at risk for the respective crystal type.
*$P < 0.05$ standard vs distal.

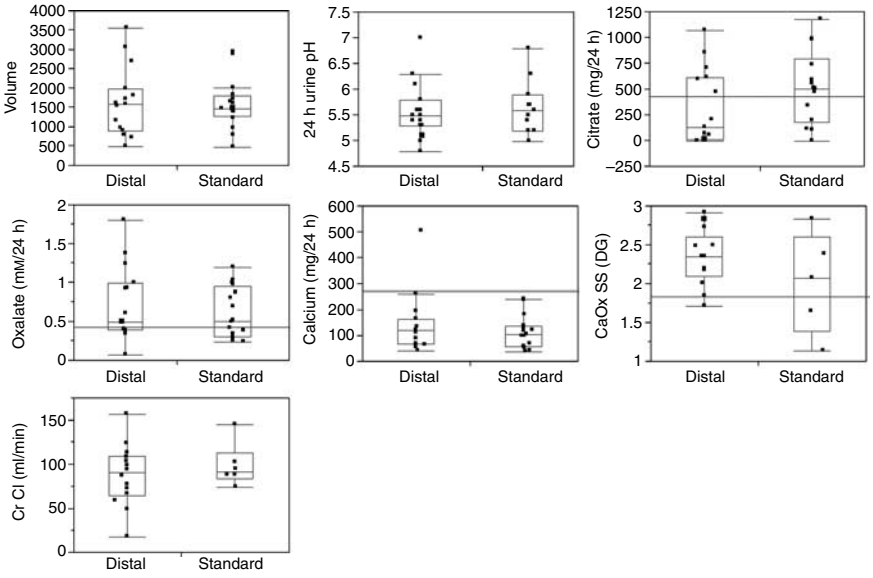

Figure 1 | Urinary chemistries in patients presenting with nephrolithiasis after RYGB. Twenty-four urine values for volume, pH, citrate, calcium, oxalate, and creatinine clearance are depicted with superimposed box plots for each analyte. Patients are divided into those undergoing distal and standard RYGB. Horizontal lines indicate upper (oxalate, calcium, CaOx SS) or lower (citrate) limits of reference ranges for selected analytes. Not all patients had sufficient data to calculate CaOx SS.

seen in the last 2 years. Mean age at time of RYGB was 48 years (range 30–61 years), preprocedure BMI was $57 \pm 12\,kg/m^2$, time to stone event was 2.2 ± 2.7 years, and decrease in BMI at the time of stone event $17.5 \pm 8.9\,kg/m^2$. Stone type was analyzed in the Mayo Clinic Metals Lab for 21 patients revealing (CaOx) in 19 patients, and mixed CaOx and uric acid (UA) in two patients. Urinary CaOx supersaturation (SS) was increased to 2.23 ± 0.50 delta Gibbs units (DG) (normal population reference mean 1.77 DG), whereas SS for UA was low (0.83 ± 3.40 DG), and absent for calcium phosphate (-1.47 ± 1.56 DG). Hyperoxaluria was a common contributing factor present in 17/31 patients (mean urinary oxalate 0.66 ± 0.40 mM/24 h).

Because the distal RYGB is associated with a shorter absorptive surface and might lead to a greater risk of malabsorption, patients were divided into standard ($n = 15$) and distal ($n = 16$) RYGB groups (Table 2). The major difference between the two subgroups was a greater presurgical BMI in the distal RYGB patients (62 vs $52\,kg/m^2$), which is not surprising because greater BMI has been a criterion for this more aggressive procedure. Twenty-four-hour citrate excretion was modestly less in the distal group (269 ± 308 vs 519 ± 388 mg; $P = 0.08$), whereas phosphorous excretion was significantly higher; other parameters including oxalate excretion did not appear to differ. Mean creatinine clearance in the entire cohort was not decreased (89 ml/min) but was less than 60 ml/min in three individuals (Figure 1). Eleven patients had a history of stones before RYGB. When analyzed as a group, those with a prior history of stones ($n = 11$) when compared with those without ($n = 20$) demonstrated a possible trend toward higher excretions of calcium (153 ± 28 vs 120 ± 21 mg/24 h; $P = 0.18$) and citrate (491 ± 116 vs 378 ± 84 mg; $P = 0.22$), but lower excretion of oxalate (0.55 ± 0.08 vs 0.73 ± 0.12 mM/24 h; $P = 0.10$). However, none of these trends reached statistical significance (Figure 2).

Ten patients had follow-up visits to our stone clinic after being placed on treatments that varied but typically included low-fat, low-oxalate diets, and use of calcium binders with meals. Overall, urinary CaOx SS decreased from 2.69 ± 0.25 to 2.12 ± 0.37 DG ($P < 0.01$), even though mean urinary oxalate excretion actually increased in the group as a whole (0.77 ± 0.34–0.86 ± 0.38 mM/24 h). When examined by individual, however, urinary oxalate excretion decreased in many (5/9 standard and 3/5 distal RYGB patients), and CaOx SS decreased in all six patients for whom data were available to calculate the CaOx SS (although for only one patient did CaOx SS decrease below the reference mean while on a treatment program).

At the time of this report, a single male patient with a history of CaOx stones had been followed in the Mayo Stone Clinic before and after the RYGB procedure. Preoperatively, hypercalciuria, hyperuricosuria, and mild hyperoxaluria were all present and accordingly he was treated with a combination of thiazide diuretics, allopurinol, and dietary advice. Although these medications were stopped at the time of the RYGB, urinary calcium, oxalate, and UA were all in the normal range 5 months postoperatively. By 11 months postoperatively, urinary oxalate excretion had increased to 0.56 mM/24 h and was at 0.66 mM/24 h 15 months postoperatively. Based on this anecdotal observation, we examined urinary oxalate excretion as a function of time after RYGB in the group of patients with nephrolithiasis. In general, 24 h urinary oxalate excretion was low in those

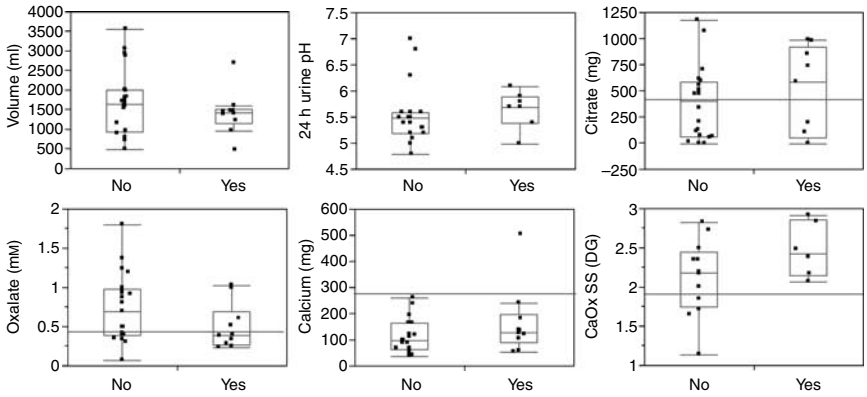

Figure 2 | Urinary chemistries in patients presenting with nephrolithiasis after RYGB divided into those without (No) or with (Yes) a prior history of stones. Twenty-four urine values for volume, pH, citrate, oxalate, calcium, and CaOx SS are depicted with superimposed box plots for each analyte. Horizontal lines indicate upper (oxalate, calcium, CaOx SS) or lower (citrate) limits of reference ranges for selected analytes. Patients are divided into those without stones before RYGB and those with antecedent stones. Among those with a prior history of stones, possible trends were for higher mean citrate ($P = 0.22$) and calcium ($P = 0.18$) excretions and lower oxalate excretions ($P = 0.10$), although none reached statistical significance. Urinary CaOx SS were equally high in both groups. Not all patients had sufficient data to calculate CaOx SS.

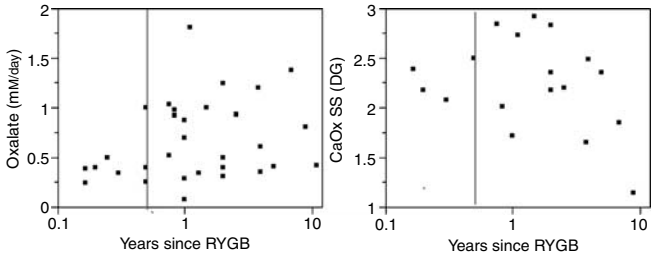

Figure 3 | Oxalate excretion among patients that presented with nephrolithiasis as a function of time since RYGB. Urinary oxalate excretion was low in many patients early after RYGB (6/8 <6 months postoperative in the left panel), whereas CaOx SS was in general high at all time points after the procedure (right panel). Note log scale on the *x* axis; vertical line is at 6 months (0.5 years). Not all patients had sufficient data to calculate CaOx SS. Urinary oxalate levels were elevated in a greater percentage of patients that presented with stones >6 months after RYGB (15/23) as compared with those <6 months after RYGB (2/8), with overall higher oxalate excretions (0.74 ± 0.42 vs 0.44 ± 0.24 mM/24 h; $P < 0.05$).

patients that presented and were studied in the early postoperative period, but increased thereafter, although CaOx SS was equally increased across all times (Figure 3). Patients were therefore divided into an early postoperative group (defined as those less than 6 months after RYGB, $n = 8$) and those further out from the procedure (>6 months; $n = 23$). As expected, the early group had lost less weight (BMI change 10 ± 3 vs 20 ± 10 kg/m^2). Urinary oxalate excretion was increased in a greater percentage of patients that presented with stones >6 months after RYGB, as compared with those <6 months after RYGB, with overall higher oxalate excretions (0.74 ± 0.42 vs 0.44 ± 0.24 mM/24 h; $P < 0.05$). However, CaOx SS was equally high in both groups (2.28 ± 0.19 vs 2.22 ± 0.58 DG), largely owing to a lower 24 h urine volume (1223 ± 413 vs 1747 ± 812 ml; $P < 0.05$) as well as a lower magnesium excretion among the patients in the earlier postoperative period.

We could not determine, from these observations in a stone clinic population, how common hyperoxaluria might be before or after RYGB. Therefore, we performed a small cross-sectional study of patients seen at Mayo Clinic pre- and post-RYGB surgery. This included patients undergoing preoperative assessment ($n = 20$) and follow-up visits after surgery at 6 months ($n = 8$) or 12 months ($n = 13$). Patients were recruited randomly over the course of several weeks in order to represent all three time periods. At baseline in this obese population (mean BMI 48 ± 8 kg/m^2), hyperoxaluria was present in only 2/20 patients (group mean 0.35 mM/24 h) and mean CaOx SS was below the reference mean (Table 3). Changes in the urinary composition were minimal at 6 months, but in the 12-month group significant decreases in urinary citrate and calcium were observed, as was an increase in urinary oxalate (mean urinary oxalate 0.74 mM/24 h; Table 3). At 12 months postoperatively, hyperoxaluria was present in 7/13 subjects and the resulting SS for CaOx was increased dramatically above the reference mean in 12 of 13 patients (mean CaOx SS of 2.38 ± 0.49 DG at 12 months vs 1.51 ± 0.78 DG at baseline; $P = 0.009$ for comparison of the two groups; Figure 4). Therefore, the risk for CaOx stones appears markedly increased in the group 1 year after RYGB as compared with the preoperative group. Because obesity is a known risk factor for renal stones, it is not surprising that nephrolithiasis was commonly present preoperatively in this RYGB patient population (14 of the 41 patients were previous stone formers). However, even when these patients with preexisting nephrolithiasis were removed from the analysis, hyperoxaluria was present in five out of eight patients at 12 months after RYGB (mean urinary oxalate 0.83 ± 0.46 mM/24 h).

DISCUSSION

In this paper, we report 60 patients that developed renal stones after RYGB surgery. These include 23 patients from

Table 3 | 24 h urinary composition of lithogenic substances in a cross-sectional sample of patients at baseline, 6 months, and 12 months after RYGB surgery

	Baseline preoperative (*n*=20)		6 months postoperative (*n*=8)		12 months postoperative (*n*=13)	
	Mean	(s.d.)	Mean	(s.d.)	Mean	(s.d.)
Volume	1939	(762)	1409	(894)	1629	(823)
pH	5.95	(0.38)	5.81	(0.92)	5.76	(0.59)
Citrate	660	(277)	563	(449)	444	(376)
Oxalate	0.35	(0.18)	0.32	(0.15)	*0.74	(0.44)
Calcium	206	(111)	*111	(86)	*112	(92)
UA	708	(255)	*426	(108)	*461	(166)
Magnesium	113	(55)	92	(58)	156	(126)
Phosphorous	1149	(580)	*716	(227)	900	(266)
Sodium	199	(98)	*118	(72)	171	(103)
Potassium	63	(21)	*35	(11)	53	(34)
Chloride	188	(102)	*114	(63)	171	(109)
Sulfate	24.7	(10.5)	*12	(6.7)	*15.9	(8.6)
CaOx SS	1.51	(0.78)	1.49	(1.31)	*2.38	(0.49)
BR SS	−0.31	(1.18)	−1.38	(1.83)	−0.92	(1.54)
UA SS	1.43	(2.81)	1.82	(4.06)	1.26	(3.63)
Creatinine clearance	117	(44)	110	(26)	99	(40)

BR, brushite; CaOx, calcium oxalate; SS, supersaturation; UA, uric acid.
*$P<0.05$ vs baseline; see Table 2 for normal reference ranges.

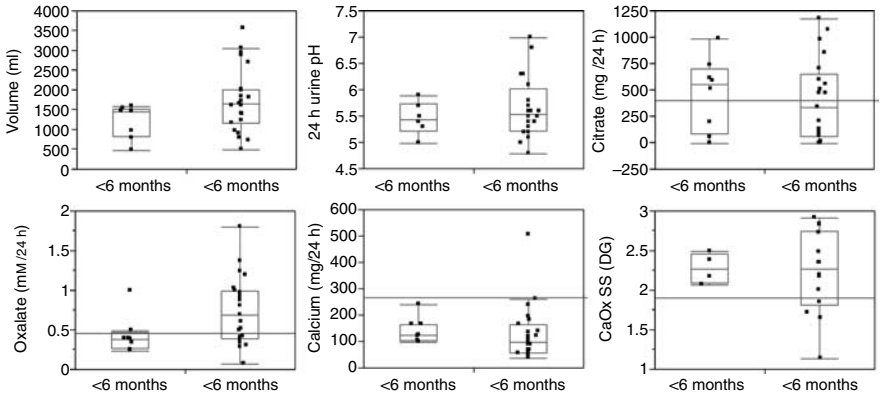

Figure 4 | Urinary chemistries among patients that presented with nephrolithiasis after RYGB as a function of time after RYGB. Twenty-four urine values for volume, pH, citrate, calcium, oxalate, and creatinine clearance are depicted with superimposed box plots for each analyte. Horizontal lines indicate upper (oxalate, calcium, CaOx SS) or lower (citrate) limits of reference ranges for selected analytes. Patients were divided in those less than 6 months vs greater than 6 months postoperative. Although oxalate levels were lower in the early postoperative group, urinary CaOx SS were equally high in both groups. Horizontal lines indicate limits of reference range for individual analytes. Not all patients had sufficient data to calculate CaOx SS.

our previous study.[22] A subset of 31 patients was seen in the Mayo Stone Clinic and urinary data were available for detailed analysis. Hyperoxaluria was a common risk factor in these stone-forming patients, although low urinary volumes and reduced 24 h urinary excretions of citrate and magnesium appear to be important contributing factors as well. Even though the RYGB operation with a Roux limb <150 cm in length is generally believed not to cause fat malabsorption, these data suggest that hyperoxaluria may indeed occur, at least in a subset, and represent a risk for CaOx nephrolithiasis. In fact, our pilot data among a cross-section of randomly selected patients suggest that approximately half may have significant hyperoxaluria 1 year after RYGB (Figure 4). Urinary calcium excretion also tended to be low in both stone-forming and non-stone-forming patients after RYGB, also consistent with some degree of fat malabsorption.

A relatively high percentage of patients that presented with nephrolithiasis after RYGB (10/31; 32%) had a prior history of stones, perhaps because obesity is a risk factor for nephrolithiasis[23] or possibly because pre-existing nephrolithiasis increases the risk for stones after RYGB. However, a similar percentage of patients in the random sample of patients undergoing the procedure also had pre-existing stones (14/41; 34%), suggesting that the obese population undergoing RYGB is indeed enriched with stone formers. It is also unclear how many of such patients with pre-existing renal stones might experience a quiescent course after RYGB, or the relative risk of stone occurrence/recurrence after other forms of gastrointestinal surgery. Although obesity is associated with increased oxalate excretion, the urinary changes we observed are not likely to be due to obesity alone. In a study from the United States,[24] urinary oxalate

was increased in obese (>120 kg) men (0.37 vs 0.50 mM/24 h) and obese (>100 kg) women (0.28 vs 0.37 mM), whereas in a German report,[25] oxalate levels were increased in obese (BMI >30 kg/m^2) women (0.45 vs 0.32 mM) but not in obese (BMI >30 kg/m^2) men (0.33 vs 0.36 mM). The increases in urinary oxalate we observed after RYGB were in general much higher (mean oxalate excretion 0.66 mM/ 24 h). Further, the mean oxalate excretion among a random cross-section of obese patients before RYGB surgery was only 0.35 ± 0.18 mM/24 h (Table 3). Finally, obesity is associated with higher rather than lower excretions of calcium and citrate.[24,25]

The findings in patients after RYGB may or may not parallel observations in patients who had undergone previous ileal or jejuno-ileal bypass procedures for hypercholesterolemia or medically complicated obesity, respectively, in whom a markedly increased incidence of renal stones, nephrocalcinosis, and renal failure was observed.[26–32] Jejuno-ileal bypass is a more extensive, malabsorptive procedure, and hyperoxaluria is secondary to hyperabsorption of oxalate from the bowel with increased urinary excretion of oxalate by the kidney.[32] In contrast, RYGB as performed today is not a global malabsorptive procedure,[26] and although nephrolithiasis was a well-known complication of the jejuno-ileal operation,[33,34] until recently it had not been recognized as a potential complication of RYGB.[22] Our results suggest that hyperoxaluria is indeed a common underlying risk factor in those RYGB patients that do develop stones, whereas hypocitraturia and a decreased 24-hr urine volume is also a contributing factor.

Enteric hyperoxaluria, observed often in association with fat malabsorption, is believed to develop when oxalates derived from the diet are delivered to the colon uncomplexed with calcium. This phenomenon is observed commonly when disorders such as Crohn's disease affect the ileum, or when the ileum has been resected, leading to bile acid and fat malabsorption. The mechanism by which RYGB patients develop hyperoxaluria has yet to be determined, but it seems likely that the length of the common channel may predispose to clinically significant fat malabsorption in some, leading to enteric hyperoxaluria. Previous studies have suggested that the degree of hyperoxaluria corresponds with the degree of steatorrhea,[35] as observed in various disease conditions associated with fat malabsorption, including inflammatory bowel disease, ileal resection, and jejuno-ileal bypass.[36–39] In the one patient among our current series in whom it was measured, 72 h fecal fat was increased (57 g), despite the absence of diarrhea. Interestingly, none of the 31 patients seen in stone clinic with nephrolithiasis after RYGB reported symptoms of diarrhea. In a single case series, steatorrhea was reported in 18 out of 45 patients after biliopancreatic bypass for obesity, although clinical symptoms were not reported.[40]

Typical treatment strategies for enteric hyperoxaluria are prescription of a low-fat, low-oxalate diet, generous fluid intake, and use of oral oxalate binders such as calcium. Previous studies have demonstrated a decrease in urinary oxalate excretion when dietary calcium content was increased or when oral calcium supplements were prescribed among patients with enteric hyperoxaluria secondary to inflammatory bowel disease, ileal resection, or jejuno-ileal bypass.[37,38,41] These dietary modifications, however, may be difficult to achieve. Although none of the patients evaluated in our stone clinic felt they had diarrhea, many have learned to alter their eating patterns toward many small meals in order to avoid symptoms. Dietary oxalate is found in green leafy vegetables, chocolate, nuts, strawberries, and soy products;[42] however, accurate information regarding the oxalate content in particular foods is difficult to find, because it is not measured routinely or listed on food labels. In addition, published values are general estimates because oxalate content can vary depending on conditions during growth or manufacture. Therefore, avoiding high oxalate intake can be a difficult proposition. Further, use of calcium as an oxalate binder can be challenging when the food is ingested via frequent snacks as opposed to larger meals. Studies to identify improved strategies to decrease urinary oxalate levels among the ever-expanding pool of patients undergoing RYGB surgery are clearly needed.

Endogenous intestinal flora utilize oxalate and could thereby limit absorption.[43] *Oxalobacter formigenes*, a normal commensurate part of the human gut microflora, can metabolize oxalate as an energy source; indeed, several studies have suggested that colonization with *O. formigenes* has a protective effect against increased oxalate excretion.[44,45] Whether or not RYGB procedures alter colonization with this organism is unknown. This point is pertinent because a single study demonstrated decreased intestinal colonization with these oxalate-degrading bacteria in patients after jejuno-ileal bypass.[46] Other intestinal bacteria could also alter intestinal oxalate absorption, either via degradation or effects on mucosal absorption. A recent study demonstrated that oral administration of a preparation of lactic acid bacteria reduced urinary oxalate excretion by a small but significant percentage in a group of patients with enteric hyperoxaluria. Oral administration of *Oxalobacter* or the active enzymes represents another promising treatment strategy because rats colonized with *Oxalobacter* changed from net colonic absorbers of oxalate to net secretors.[47]

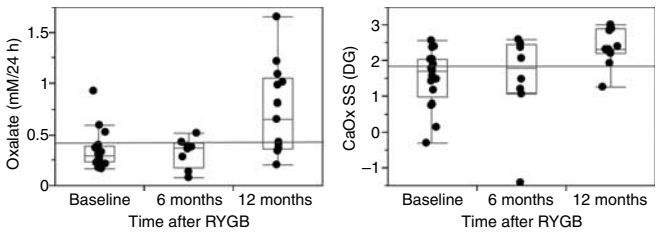

Figure 5 | Changes in urinary oxalate and CaOx SS in a random sample of patients both before and after RYGB. Oxalate was increased above the upper limit of the reference range (horizontal line, 0.46 mM/ 24 h) in two out of 20 patients preprocedure and in seven out of 13 at 12 months. At 12 months, all but one patient had a CaOx SS above the reference mean of 1.77 (horizontal line). $P = 0.009$ for comparison of CaOx SS between baseline and 12 months groups.

The true prevalence of hyperoxaluria after RYGB is unknown and would require larger prospective urine studies in non-stone formers as well as stone formers. Our preliminary data in a small cross-section of patients after RYGB suggest that hyperoxaluria may be quite common (Figure 5). Given the increasing use of this procedure primarily as a treatment for morbid obesity (108 000 in 2003[21]), such studies to define the prevalence of hyperoxaluria after RYGB are clearly needed. The cross-sectional data also indicate that hyperoxaluria is not present in the majority of patients at 6 months after surgery, nor was hyperoxaluria common in those stone patients that presented <6 months after surgery. The reasons are not certain, but could involve dietary changes over time after RYGB.

A very recent report lists urinary tract calculus as a common cause for emergency room visits (3.6%) and readmission to hospital (3.0%) within the first 180 days after bariatric surgery.[48] However, the incidence of renal stones over the course of many years after this procedure is also unclear. Our study suggests that the risk may be clinically important, especially in the group undergoing a distal malabsorptive RYGB, as our previous study revealed that 16% of distal RYGB patients developed a stone after a mean of 48 months since the surgery (range 12–148 months).[22] It is notable that a high percentage of the stone patients had pre-existing stones (32%). We are not able to provide any accurate estimate of the risk of stone occurrence after the procedure, as the larger group of patients undergoing the standard RYGB were not surveyed to identify stone events not treated at Mayo Clinic. However, as the average number of stone events among those with a pre-existing stones was only 1.3, it seems less likely that the cases we now report after RYGB simply represent the natural history of an underlying stone diathesis. In long-term follow-up of a large cohort patients after jejuno-ileal bypass from a single center, the cumulative incidence of renal stones over 15 years was 29%, whereas the cumulative incidence of renal insufficiency was 9% over the same time period.[49] Indeed, oxalate deposition in the renal parenchyma leading to renal failure followed by systemic oxalosis was a known complication after jejuno-ileal bypass[49] and there is a case report of this complication after RYGB.[22] Therefore, the prevalence of clinical renal disease after RYGB, including nephrolithiasis, could potentially increase over time as more patients are operated on and accrue time at risk after surgery. If the incidence and severity of enteric hyperoxaluria in this study is confirmed in prospective evaluation of larger numbers of patients, preventative treatment strategies may be necessary in all patients following RYGB. At this point, we recommend that all patients who develop renal stones after RYGB have prompt metabolic evaluation and potential treatment for stone prevention. Although increased risk for hyperoxaluria or nephrolithiasis should be considered during the preoperative assessment for RYGB, we would not currently consider this a contraindication for the procedure.

In conclusion, hyperoxaluria is common among patients after RYGB, especially those more than 6 months after the procedure, and is a risk for CaOx-stone formation. Further, patients may present with stones even in the first 6 months after RYGB, often manifesting with markedly increased urinary CaOx SS owing to a combination of lower volumes and more modest hyperoxaluria. Effective measures to reduce urinary oxalate excretion will be necessary to reduce urinary SS and hence stone recurrence rate in this patient population. Further studies are needed to define the incidence of these urinary changes and stone formation as well as the cause of hyperoxaluria in the RYGB population.

MATERIALS AND METHODS

All patients seen at Mayo Clinic, Rochester, since 1985 who had been diagnosed with nephrolithiasis, oxalate nephropathy, or enteric hyperoxaluria were identified as described previously.[22] This patient list was queried to identify all patients with a diagnoses of obesity or RYGB, including all patients contained in a clinical database of consecutive patients who have undergone bariatric surgery at Mayo Clinic, Rochester, between 1985 and October 2004 ($n=1436$). Additional patients in the Mayo system suffering nephrolithiasis after RYGB were identified via a mail-out survey sent to that subset of patients having undergone distal RYGB at our institution and from a query of diagnoses of patients referred to the Mayo Stone Clinic through early 2006. Table 1 shows breakdown of patients. The complete Mayo Clinic records were reviewed to confirm that patients had undergone RYGB at Mayo or elsewhere and to verify the presence of symptomatic nephrolithiasis after the procedure. In this manner, a total of 60 patients were identified who suffered nephrolithiasis events after RYGB and form the basis of this report.

A cross-sectional study was also completed among patients seen in the Mayo Endocrinology Clinic for RYGB surgery. Patients routinely undergo a complete preoperative assessment as well as 6- and 12-month follow-up visits. Patients were randomly recruited over the course of several weeks to collect 24-h urine SS studies in order to represent all time periods.

For each patient, the medical record was abstracted for the following information: age at time of RYGB, BMI at RYGB and at time of occurrence of symptomatic nephrolithiasis, history of pre-RYGB kidney stones, number of stones pre- and post-RYGB, time to development of first stone post-RYGB, number of stones per year, and interventions required. The type of bariatric procedure was also classified as a standard RYGB with <150 cm Roux limb length[50] or distal RYGB (also termed a very, very long limb RYGB), a modification of RYGB establishes a short common channel of <125 cm distal ileum within which all enzymatic digestion of complex carbohydrates, proteins, and fats occurs and thus has malabsorptive components.[51] Additionally, we captured all available laboratory studies including serum creatinine concentration, creatinine clearance, and 24-h urine studies (including volume, pH, total excretions of citrate, oxalate, sodium, potassium, calcium, phosphorous, UA, chloride, creatinine, sulfate, and magnesium, and SS of CaOx, brushite, apatite, UA, and sodium urate). Reference means were obtained from a normal value study conducted in non-stone-forming adults. Follow-up 24-h urine studies were also captured after treatments that included diet alone (low oxalate, generous calcium, low fat, increased fluids), or diet combined with medications including oxalate binders.

Patient demographics and biochemical information were analyzed using the JMP software package (SAS Institute, Cary, NC, USA). Results are expressed as means $\pm$ s.d. and box plots for each

patient group. $P<0.05$ were deemed significant for comparison *t*-tests.

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